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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,277	08/20/2001	Peter Jozef Leo Hespel	702-010802	6608

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EXAMINER	
GOLLAMUDI, SHARMILA S	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 06/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,277	HESPEL, PETER JOZEF LEO	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-18,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-18,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Supplemental Response and Amendments to the Claims received on April 2, 2004 is acknowledged. Claims **13-18 and 21-22** are pending in this application. Claims 1-12 and 19-20 are cancelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 13-18 and 21-22 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of muscle disuse syndrome, does not reasonably provide enablement for prevention of muscle disuse syndrome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims is withdrawn in view of the amendments.

Claim Rejections - 35 USC § 102

The rejection of claims 13, 15-18, and 21 under 35 U.S.C. 102(b) as being anticipated by Elgebaly (5,091,404) withdrawn in view of the amendments.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13-18 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/00148 (entire document).

WO discloses the administration of creatine for the therapeutic use of improving muscle mass, muscle function, muscle stamina, shortening the recovery after physical strain after post-operative muscle atrophy, treatment of heart complaints, different types of myopathy and cachectic states. See abstract and especially claim 9. WO discloses one dose administered three times a day of 9 grams of creatine (total daily dose)f or one week, followed by a maintenance dose of 3 grams of creatine in a unit dose once a day. See page 13 of translation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 13-18 and 21 under 35 U.S.C. 103(a) as being unpatentable over Pischel et al (5,863,939) in view of Howard et al (5,968,544) is maintained.

Pischel et al teach a method of administering creatine ascorbates for enhancing muscular development, as a prophylactic against and treatment for ischemia and muscular atrophy. See abstract. The dosage form may be as an oral supplement or intravenous. See column 1, line 56.

Pischel et al do not specify the dosage wherein the amount of creatine is decreased upon treatment.

Howard et al teach a composition containing creatine. The reference discloses that 20-30 grams creatine per day for several days can lead to a greater than 20% increase in human skeletal muscle. Howard discloses that after several days of 20 grams of creatine supplementation, it takes no more than 2 to 3 grams per day to maintain the saturation of body stores. See column 1, lines 40-50 and column 3, lines 10-20. Howard teaches dividing the dose during the day.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Pischel et al and Howard et al and utilize a high creatine loading, followed by a decrease dosage phase. One would be motivated to look to the teachings of Howard et al since Howard teaches the general principle of creatine supplementation and its subsequent utilization in the body. Howard discloses that an increased loading of creatine for several days increases skeletal muscle and creatine saturation is attained. The creatine supply in the body is

maintained with a lower dosage. Therefore from Howard's teachings, it is deemed obvious to a skilled artisan that once saturation of a substance is attained in the body, the excess is excreted; thus maintaining the same dosage once saturation has been reached is useless. Further motivation is that Howard discloses that during the high loading phase, increase in skeletal muscles and strength is observed. Therefore since muscle atrophy is characterized by decreasing strength and size of muscles after inactivity, one would be motivated to use Howard's creatine dosage with a reasonable expectation of success of treating Pischel's muscle atrophy.

Response to Arguments

Applicant argues that argues that muscles disuse syndrome is defined as " a temporal disorder caused by lack of neuromuscular stimulation consequent to lack of muscle activity which can reversed. Applicant recognizes that Pischel et al disclose creatine for enhancing muscular development and strength in athletes, as prophylatics against ischemia, as immune system stimulants, and for treating muscular atrophy. However, it is argued that the definition of muscle disuse is not disclosed by Pischel et al. Applicant argues that muscle atrophy is a disorder that is characterized by irreversible loss of muscle tissue that is replaced by connective tissue. Applicant argues that the secondary reference Howard et al do not disclose the dosage for muscle disuse syndrome in particular. Applicant vaguely argues unexpected results.

Applicant's arguments have been fully considered but they are not persuasive. Firstly, as recognized by the applicant, Pischel et al teach the use of creatine t treat muscular atrophy. Applicant incorrectly asserts that muscular atrophy is only associated

characterized by irreversible loss of muscle tissue. Webster's dictionary defines atrophy as: decrease in size or wasting away of a body part or tissue. This definition does not contain applicant's assertion of irreversible muscle loss. Furthermore, the examiner cites art of interest that clearly demonstrates that link between muscular atrophy and immobilization. US patent 4,635,931 states that "It has long been well known that persons which for some reason have been bedridden for a long period of time run the risk of contracting special diseases caused by confinement to the bed and the relative immobility this means. Examples of such diseases are thrombosis, muscular atrophy, and skeletal decalcification." See column 1, lines 1-10.

Additionally, the examiner is confused by applicant's arguments that atrophy has nothing to do with immobilization when the instant specification page 1 discloses that "the degenerative symptoms typical to muscle disuse syndrome include muscle atrophy, reduced maximal power, premature muscle fatigue, and reduced muscle energy stores". Applicant further defines muscular atrophy as decreased muscle volume. On lines 27-33 of instant specification, applicant states that when a muscle is immobilized, atrophy is clearly visible by slimming of the legs. Pischel disclose the use of creatine for muscular atrophy, the references states on column 1, lines 44-50 that "it [creatine] has been known for hundred years as a muscular substance and serves as a source of energy for the muscle. It was shown in a series of scientific studies that the intake of creatine can lead to increase in muscular tissue and muscular performance.

In regards to the applicant's repeated argument stating difference between disease and immobilization, the examiner is confused by this argument since not only

does the instant specification on page 1 clearly state that "muscle disuse syndrome may occur in any skeletal muscle subject to reduced mechanical loading due to whatever causes....[such as] disease condition, aging, physical/mental handicap, forced bedrest , or reduced level of physical activity", applicant claim 18 recites diseases as part of the Markush group ins which muscle disuse syndrome is a results. The examiner additionally points out that the cause per se of a syndrome, i.e. disease versus physical inactivity, does not impute patentable difference to claim unless it imparts a different characteristic than that known in the art. It is the examiner's position that there are key features of muscle disuses syndrome such as atrophy, decreased muscle energy, fatigue, etc, regardless of the reasons why the muscle is not being utilized.

Thus, Pischel clearly teaches the therapeutic use of creatine for the symptoms of muscle disuse and thus would implicitly treat muscle disuse syndrome.

In regards to Howard et al, Howard is relied upon to specifically teach the dosage of creatine. Thus, Howard does not have to teach the broad teaching of the invention since this is covered by the primary reference. Howard provides the background in creatine and how the dosage effects the body. Firstly, Howard teaches that creatine occurs in skeletal muscles and plays an important role in the regulation of skeletal muscle energy metabolism and it known that phosphocreatine availability is important to the continuation of muscle force production. Again, the examiner reiterates that the instant specification characterizes muscle disuse with decreased energy stores and muscle fatigue. Howard states that the after high loading creatine into the body, less

creatine is needed to maintain the creatine in saturated amounts in the body. See column 1 in its entirety.

Therefore, clearly Howard provides the motivation to dose accordingly, with a high loading followed by decreased amounts. It is further the examiner's position that one would dose until improvement is seen. Further, it should be noted that "up to" in the recitation "up to ten weeks" includes the numerical value zero.

It should be noted that differences in dosage amounts does not impart patentability unless applicant demonstrates criticality of these amounts. Applicant has vaguely mentioned unexpected results without substantiating this assertion. Therefore, applicant has not overcome the obviousness rejection.

The rejection of claims 13-14, 16-18, and 21-22 under 35 U.S.C. 103(a) as being unpatentable over XP-00210314 in view of Howard et al (5,968,544) is maintained.

Wyss et al teach the oral creatine supplementation in muscle disease such as Duchenne and Becker muscular dystrophy, spinal muscular atrophy, etc. See page 334. Wyss discloses that in various muscle diseases the intracellular concentration of creatine and phosphocreatine decreases. See page 334. Wyss teaches two creatine supplement approaches. One being a continuous supplementation of creatine and the other being intermittent short-period supplementation with high doses of creatine. Wyss teaches that the intermittent dosage is favorable since extra creatine can be taken into the muscle cells, which is followed by discontinuing in order to allow recovery of the

creatine transporter activity. Wyss teaches an experiment wherein an oral creatine supplement was given to a DMD patient for 155 days. See page 335.

Wyss does not specify the creatine dose.

Howard et al teach a composition containing creatine. The reference discloses that 20-30 grams creatine per day for several days can lead to a greater than 20% increase in human skeletal muscle. Howard discloses that after several days of 20 grams of creatine supplementation, it takes no more than 2 to 3 grams per day to maintain the saturation of body stores. See column 1, lines 40-50 and column 3, lines 10-20. Howard teaches dividing the dose during the day.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Wyss et al and Howard et al and utilize a high creatine loading, followed by a decrease dosage phase. One would be motivated to look to the teachings of Howard et al since Howard teaches the general principle of creatine supplementation and its subsequent utilization in the body. Howard discloses that an increased loading of creatine for several days increases skeletal muscle and creatine saturation is attained. The creatine supply in the body is maintained with a lower dosage. Further motivation is that Howard discloses that during the high loading phase, increase in skeletal muscles and strength is observed. Therefore since muscle disease is characterized by decreasing strength and size of muscles after inactivity, one would be motivated to use Howard's creatine dosage with a reasonable expectation of success.

Response to Arguments

Applicant argues that the claimed invention is directed to treating muscle disuse syndrome defined as " a temporal disorder caused by lack of neuromuscular stimulation consequent to lack of muscle activity which can reversed." The applicant states that the prior art does not discloses this definition. Applicant argues that Howard does not teach the specific dosage wherein at least 5g is administered and decreased to 5g and lasts no longer than 10 days.

Applicant's arguments have been fully considered but they are not persuasive. Firstly, the examiner points out that the applicant's argued definition does not appear in the claims. Applicant merely claims a method for treating skeletal muscle subjected to immobilization, which results in muscle disuse syndrome, the scope of this recitation is broad. For instance, XP teaches the use of creatine for muscular dystrophy and muscular atrophy. Although applicant argues that in dystrophy the muscle cells undergo destruction, the instant scope stills reads on dystrophy. Dystrophy causes immobilization since the patient muscle functioning capacity decreases to the point of lack of use. This immobilization in turn causes the symptoms associated with disuse syndrome such as atrophy, decrease in energy stores, etc.. The examiner cites US patent 5,604,199 as art of interest to support the examiner's assertion that dystrophy is accompanied by muscle wasting and immobilization of the skeletal muscles. The reference states that muscular dystrophy such as BMD and DMD exhibits progressive muscle weakness and wasting and that patients at some point lose the ability to walk . See column 1. Further, nowhere do the claims recite temporary immobilization. The

examiner additionally notes claim 18 wherein it is claimed that the disuse syndrome is caused by disease or handicap, as it can be seen dystrophy falls into this scope. Therefore, the prior art reads on the instant scope of the claims.

Arguments pertaining to Hoard have been addressed above. However, it is pointed out that the claims do not recite the dosage of ten days as argued by applicant. Further, the applicant's argument that Howard does not teach administering at least five grams and decreasing to five grams is confusing. It is the examiner's position that Howard teaches the general principle of high dosing, followed by decreased dosage to maintain the creatine supply in the body.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/00148 (entire document).

WO discloses the administration of creatine for the therapeutic use of improving muscle mass, muscle function, muscle stamina, shortening the recovery after physical strain after post-operative muscle atrophy, treatment of heart complaints, different types of myopathy and cachectic states. See abstract and especially claim 9. WO discloses one dose administered three times a day of 9 grams of creatine (total daily dose)f or one week, followed by a maintenance dose of 3 grams of creatine in a unit dose once a day. See page 13 of translation. WO discloses that 10mg to 10 grams of creatine a day is suitable but the optimal dosage depends on the particular use, body weight, the age, and individual condition of the consumer. See page 12.

WO does not specify utilizing 5 grams per dose.

It is deemed obvious to one of ordinary skill in the art a the time the invention was made to manipulate parameters such as dosage and treatment length depending on an array of factors such as patient profile, which includes weight, age, symptoms, severity of symptoms, and disease being treated. It is within the skill of an artisan to determine and implement the appropriate dosage and treatment length through reunite experimentation and optimization.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-

272-0614. The examiner can normally be reached on M-F (8:00-5:00) with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SSG

June 7, 2004